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PRIMARY SCLEROSING CHOLANGITIS IN AN ANTI-NEUTROPHIL CYTOPLASMIC ANTIBODY-NEGATIVE WOMAN: DIAGNOSTIC CHALLENGES IN A POSSIBLE ATYPICAL PHENOTYPE

COLANGITE ESCLEROSANTE PRIMÁRIA EM UMA MULHER COM ANTICORPO ANTICITOPLASMA DE NEUTRÓFILOS NEGATIVO: DESAFIOS DIAGNÓSTICOS EM UM POSSÍVEL FENÓTIPO ATÍPICO

COLANGITIS ESCLEROSANTE PRIMARIA EN UNA MUJER CON ANTICUERPOS ANTICITOPLASMA DE NEUTRÓFILOS NEGATIVOS: DESAFÍOS DIAGNÓSTICOS EN UN POSIBLE FENOTIPO ATÍPICO

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ABSTRACT

Primary sclerosing cholangitis is a rare chronic cholestatic liver disease characterized by inflammation, fibrosis, and multifocal stricturing of the intrahepatic and/or extrahepatic bile ducts. Although its diagnosis is usually supported by cholangiographic abnormalities and may be associated with immune-mediated conditions, atypical presentations without suggestive serological markers can delay clinical recognition. This report describes a 53-year-old woman with an uncommon presentation of primary sclerosing cholangitis, initially characterized by fever, severe abdominal pain, jaundice, acute pancreatitis with peripancreatic necrosis, persistent cholestasis, and recurrent episodes of severe acute cholangitis. The diagnostic investigation was challenging because autoimmune markers were negative, immunoglobulin G4 levels were normal, and magnetic resonance cholangiopancreatography showed only mild intrahepatic bile duct dilation without typical findings of primary sclerosing cholangitis. Definitive diagnosis was established only after endoscopic retrograde cholangiopancreatography, which demonstrated multifocal biliary strictures and irregularities compatible with the disease. The patient subsequently developed Tokyo grade III acute cholangitis, requiring intensive care, vasopressor support, broad-spectrum antibiotic therapy, and referral for liver transplantation assessment. This case highlights that primary sclerosing cholangitis may present with severe systemic manifestations, pancreatitis, negative autoimmune markers, and initially inconclusive noninvasive imaging. Persistent cholestasis of unclear etiology should maintain primary sclerosing cholangitis within the differential diagnosis, even in the absence of classical clinical, serological, or radiological findings. In selected cases, endoscopic retrograde cholangiopancreatography remains essential for diagnostic clarification and timely referral to specialized hepatology care.

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Keywords: Primary Sclerosing Cholangitis. Cholestasis. Autoantibodies. Endoscopic Retrograde Cholangiopancreatography. Acute Cholangitis. Acute Pancreatitis.

RESUMO

A colangite esclerosante primária é uma doença hepática colestática crônica rara, caracterizada por inflamação, fibrose e estenoses multifocais dos ductos biliares intra-hepáticos e/ou extra-hepáticos. Embora o diagnóstico seja geralmente sustentado por alterações colangiográficas e possa estar associado a condições imunomediadas, apresentações atípicas sem marcadores sorológicos sugestivos podem retardar o reconhecimento clínico. Este relato descreve uma mulher de 53 anos com apresentação incomum de colangite esclerosante primária, inicialmente caracterizada por febre, dor abdominal intensa, icterícia, pancreatite aguda com necrose peripancreática, colestase persistente e episódios recorrentes de colangite aguda grave. A investigação diagnóstica foi desafiadora, pois os marcadores autoimunes foram negativos, os níveis de imunoglobulina G4 estavam normais e a colangiopancreatografia por ressonância magnética mostrou apenas discreta dilatação dos ductos biliares intra-hepáticos, sem achados típicos da doença. O diagnóstico definitivo foi estabelecido apenas após colangiopancreatografia retrógrada endoscópica, que demonstrou estenoses biliares multifocais e irregularidades compatíveis com a doença. A paciente evoluiu posteriormente com colangite aguda grave grau III de Tóquio, necessitando de terapia intensiva, suporte vasopressor, antibioticoterapia de amplo espectro e encaminhamento para avaliação de transplante hepático. Este caso evidencia que a colangite esclerosante primária pode se manifestar com acometimento sistêmico grave, pancreatite, marcadores autoimunes negativos e exames de imagem não invasivos inicialmente inconclusivos. A colestase persistente de etiologia indefinida deve manter a colangite esclerosante primária no diagnóstico diferencial, mesmo na ausência de achados clínicos, sorológicos ou radiológicos clássicos. Em casos selecionados, a colangiopancreatografia retrógrada endoscópica permanece essencial para esclarecimento diagnóstico e encaminhamento oportuno para cuidados hepatológicos especializados.

Palavras-chave: Colangite Esclerosante Primária. Colestase. Autoanticorpos. Colangiopancreatografia Retrógrada Endoscópica. Colangite Aguda. Pancreatite Aguda.

RESUMEN

La colangitis esclerosante primaria es una enfermedad hepática colestásica crónica rara, caracterizada por inflamación, fibrosis y estenosis multifocales de los conductos biliares intrahepáticos y/o extrahepáticos. Aunque su diagnóstico suele estar respaldado por alteraciones colangiográficas y puede asociarse con enfermedades inmunomediadas, las presentaciones atípicas sin marcadores serológicos sugestivos pueden retrasar el reconocimiento clínico. Este reporte describe a una mujer de 53 años con una presentación inusual de colangitis esclerosante primaria, caracterizada inicialmente por fiebre, dolor abdominal intenso, ictericia, pancreatitis aguda con necrosis peripancreática, colestasis persistente y episodios recurrentes de colangitis aguda grave. La investigación diagnóstica fue compleja, ya que los marcadores autoinmunes fueron negativos, los niveles de inmunoglobulina G4 fueron normales y la colangiopancreatografía por resonancia magnética mostró solo una leve dilatación de los conductos biliares intrahepáticos, sin hallazgos típicos de la enfermedad. El diagnóstico definitivo se estableció únicamente tras la colangiopancreatografía retrógrada endoscópica, que demostró estenosis biliares multifocales e irregularidades compatibles con la enfermedad. Posteriormente, la paciente desarrolló colangitis aguda grave grado III de Tokio, requiriendo cuidados intensivos, soporte vasopresor, antibioticoterapia de amplio espectro y derivación para evaluación de trasplante hepático. Este caso destaca que la colangitis esclerosante primaria puede presentarse con manifestaciones sistémicas graves, pancreatitis, marcadores autoinmunes negativos e imágenes no invasivas inicialmente no concluyentes. La colestasis persistente de etiología

no clara debe mantener la colangitis esclerosante primaria dentro del diagnóstico diferencial, incluso en ausencia de hallazgos clínicos, serológicos o radiológicos clásicos. En casos seleccionados, la colangiopancreatografía retrógrada endoscópica sigue siendo esencial para la clarificación diagnóstica y la derivación oportuna a atención hepatológica especializada.

Palabras clave: Colangitis Esclerosante Primaria. Colestasis. Autoanticuerpos. Colangiopancreatografía Retrógrada Endoscópica. Colangitis Aguda. Pancreatitis Aguda.

1 INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic, progressive cholestatic liver disease of incompletely understood etiology, characterized by inflammation, fibrosis, and multifocal stricturing of the intrahepatic and/or extrahepatic bile ducts. It is associated with substantial morbidity and mortality and may progress to secondary biliary cirrhosis, liver failure, and the need for liver transplantation, which remains the only definitive therapy in advanced cases. In the absence of transplantation, the mean survival after diagnosis is estimated to be approximately 10 years. (MACFAUL; CHAPMAN, 2004)

The incidence of PSC ranges from 0 to 1.3 cases per 100,000 person-years, with a reported prevalence of up to 16.2 cases per 100,000 individuals, and the disease is most commonly diagnosed between the third and fourth decades of life. Approximately half of patients are asymptomatic at diagnosis, which is often established after the incidental detection of cholestatic abnormalities on routine laboratory testing. In symptomatic patients, fatigue, pruritus, and abdominal pain are the most frequent manifestations, although jaundice and signs of advanced liver disease may occur in later stages. (TABIBIAN; BOWLUS, 2017)

From a laboratory perspective, PSC typically presents with a cholestatic pattern, characterized by a predominant elevation of alkaline phosphatase, whereas aminotransferase elevations are usually mild to moderate. Etiological investigation requires exclusion of secondary causes of cholestasis and assessment of autoimmune markers, although no specific serological marker exists for PSC. Diagnosis is primarily based on characteristic cholangiographic findings, with endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) playing central roles in diagnostic confirmation. (PARLAK; ÇIÇEK; DIŞIBEYAZ; KÖKSAL; ŞAHIN, 2007)

Treatment remains challenging, as no pharmacological therapy has been proven to modify the natural history of the disease. Endoscopic interventions may be used for the management of dominant strictures, while liver transplantation remains the only curative option in patients with decompensated cirrhosis or severe disease-related complications. (LEE; KAPLAN, 1995)

We report the case of a 53-year-old female patient with an acute and systemic initial presentation characterized by fever, severe abdominal pain, and jaundice, initially managed as a suspected arboviral infection. Her clinical course was marked by severe acute pancreatitis with peripancreatic necrosis, persistent cholestasis, and subsequent episodes of severe acute cholangitis classified as Tokyo grade III, requiring admission to the intensive care unit. The prolonged diagnostic investigation revealed imaging studies without clear

mechanical obstruction and negative autoimmune markers, which delayed etiological definition. The diagnosis of PSC was established only after ERCP, several months after symptom onset, ultimately leading to referral for liver transplantation assessment.

The relevance of this case lies in its atypical and severe clinical presentation, with an initial systemic inflammatory course and associated pancreatitis, in addition to the absence of suggestive serological markers, which made diagnosis more difficult and delayed. The case highlights the importance of maintaining a high degree of diagnostic suspicion in patients with persistent cholestasis of unclear etiology, the need for stepwise investigation and multidisciplinary care, and the decisive role of ERCP in scenarios in which less invasive imaging methods are inconclusive. Therefore, this report contributes to the recognition of non-classical forms of PSC presentation, potentially associated with greater severity and adverse outcomes.

2 OBJECTIVE

The objective of this case report is to demonstrate the diagnostic difficulties associated with non-classical presentations of PSC, particularly in patients who, despite a presumed immune-mediated etiology, present with negative autoimmune markers. This diagnostic profile may delay investigation and definitive treatment, exposing the patient to complications resulting from the absence of targeted management. Therefore, careful attention to uncommon and atypical presentations of PSC is essential, and an immune-mediated etiology should remain within the diagnostic hypothesis even when autoimmune markers are negative.

3 METHODS

The information included in this case report was obtained through medical record review, patient interview, documentation of diagnostic imaging findings, and literature review.

4 CASE REPORT

A 53-year-old previously healthy female patient, with a history of self-limited psoriasis and no current treatment, was admitted to the emergency department of Hospital das Clínicas de Marília after referral from an urgent care unit. She presented with a seven-day history of myalgia, arthralgia, frontal headache associated with retro-orbital pain, documented fever up to 39 °C during the first three days, nausea, vomiting, watery diarrhea without mucus or blood, and abdominal pain. In the 24 hours preceding admission, the abdominal pain worsened significantly, becoming severe, rated 10 out of 10, predominantly located in the right

hypochondrium and radiating in a band-like pattern to the upper abdomen. This was associated with choluria and mucocutaneous jaundice. She denied acholic stools or bleeding. During the initial symptomatic period, she had been followed at a primary care unit under the diagnostic hypothesis of dengue fever, although serological confirmation was not obtained.

On hospital admission, laboratory tests showed total bilirubin of 9.9 mg/dL, direct bilirubin of 7.77 mg/dL, aspartate aminotransferase of 1,847 U/L, alanine aminotransferase of 641 U/L, amylase of 1,678 U/L, lipase of 2,446 U/L, alkaline phosphatase of 214 U/L, gamma-glutamyltransferase of 787 U/L, and mild leukocytosis of 12,020/mm³ without left shift.

Serological testing for hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus, and syphilis was negative, with evidence of previous immunity to hepatitis B. Tests for dengue, including serology and polymerase chain reaction, as well as yellow fever immunoglobulin M, zika virus, and chikungunya, were negative. A rapid test for visceral leishmaniasis was also non-reactive.

Given the elevation of pancreatic enzymes to more than three times the upper limit of normal, associated with typical abdominal pain, the diagnosis of acute pancreatitis was established. Fasting and vigorous intravenous hydration were initiated.

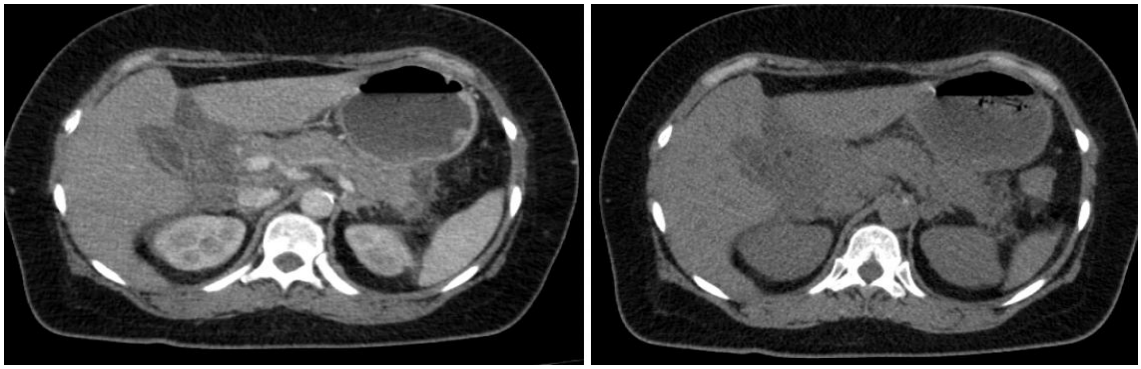
On the following day, laboratory deterioration was observed, with further elevation of aminotransferases, worsening leukocytosis, and increased C-reactive protein. The possibility of transinfectious hepatitis was considered. The patient was transferred to the intensive care unit on the same day.

As inflammatory markers remained elevated, antibiotic therapy with ciprofloxacin and metronidazole was initiated, resulting in partial clinical improvement and reduction of C-reactive protein levels. She was discharged from the intensive care unit after three days of intensive treatment. Subsequently, she developed new laboratory deterioration, leading to escalation of antibiotic therapy to piperacillin-tazobactam and prompting additional imaging investigation.

Contrast-enhanced abdominal computed tomography demonstrated hepatomegaly with a simple hepatic cyst in segment II, measuring 2.0 × 1.7 cm, absence of biliary tract dilation, gallbladder wall thickening without gallstones, and an enlarged heterogeneous pancreas associated with peripancreatic fat stranding and an extensive fluid collection suggestive of a forming pseudocyst.

Figure 1

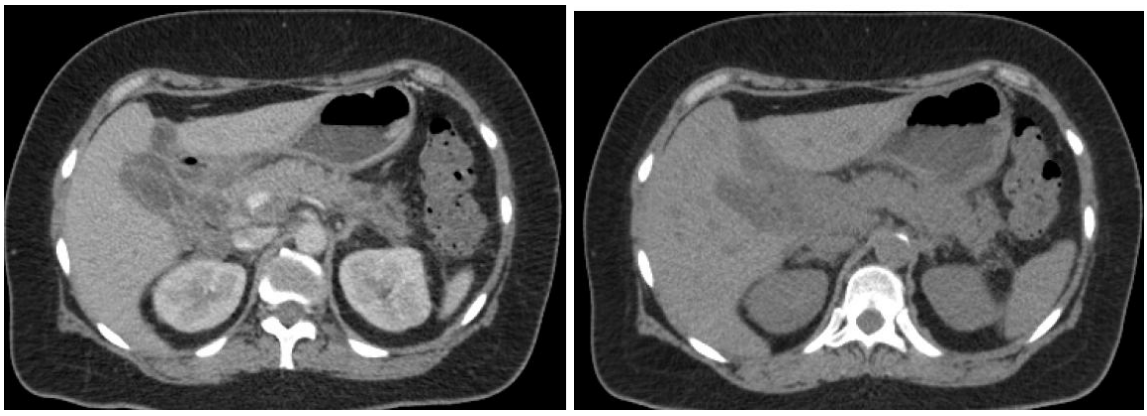
Contrast-enhanced abdominal computed tomography demonstrating hepatomegaly, gallbladder wall thickening, an enlarged heterogeneous pancreas with peripancreatic fat stranding, and extensive peripancreatic fluid collection suggestive of a developing pseudocyst



The patient partially responded to piperacillin-tazobactam but developed fever again, leading to a repeat contrast-enhanced abdominal computed tomography. The findings were similar to those of the previous examination, now with minimal dilation of the intrahepatic bile ducts in the left hepatic lobe. She evolved without further febrile episodes, with clinical and laboratory improvement, and was discharged with referral for outpatient follow-up by the internal medicine team.

Figure 2

Contrast-enhanced abdominal computed tomography demonstrating minimal dilation of the intrahepatic bile ducts, in addition to findings similar to those observed in the previous computed tomography examination



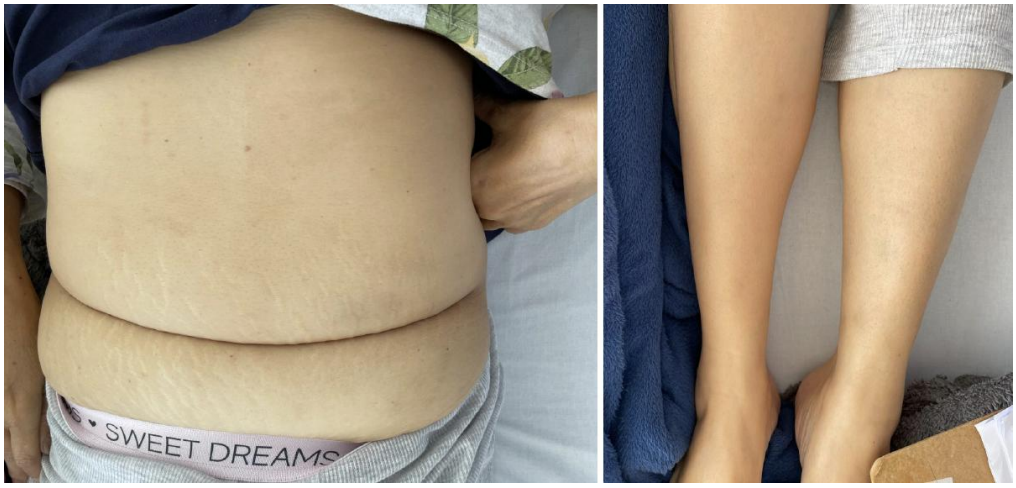
Second Hospitalization

After outpatient evaluation, the patient returned with symptoms that had begun weeks after discharge, including postprandial abdominal distension, hyporexia, weight loss of 10 kg,

progressive jaundice, choluria, acholic stools, and generalized pruritus. She denied abdominal pain or fever.

Figure 3

Mild jaundice involving the trunk and lower limbs.

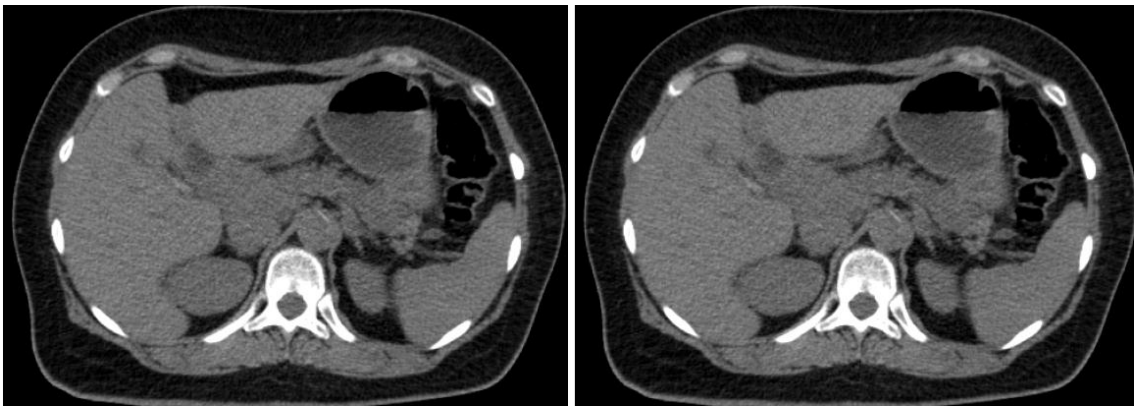


Laboratory tests revealed a marked cholestatic pattern, different from that observed during the previous hospitalization, with alkaline phosphatase of 990 U/L, gamma-glutamyltransferase of 2,135 U/L, total bilirubin of 2.15 mg/dL, direct bilirubin of 1.56 mg/dL, and mild aminotransferase elevation.

Abdominal computed tomography showed mild intrahepatic bile duct dilation, predominantly in the left hepatic lobe, without identifiable mechanical obstruction.

Figure 4

Contrast-enhanced abdominal computed tomography demonstrating mild intrahepatic bile duct dilation, predominantly in the left hepatic lobe



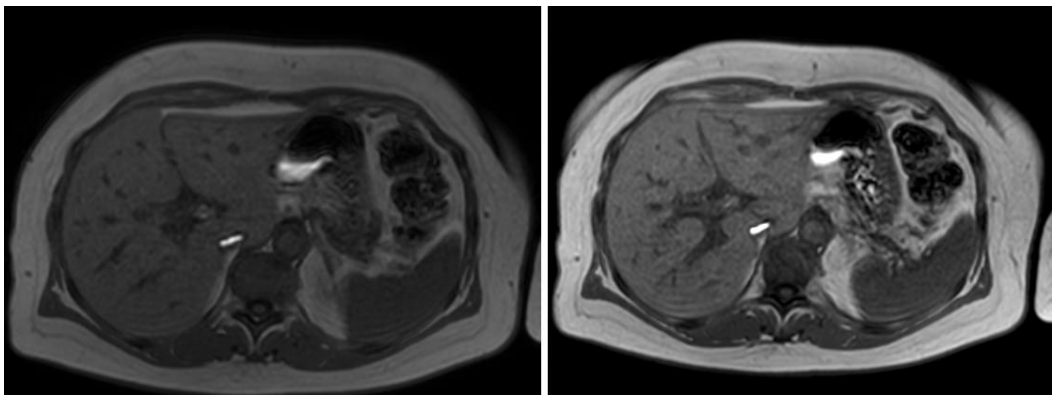
The patient was evaluated by the surgical gastroenterology team, which considered the possibility of extrahepatic biliary obstruction secondary to edema related to previous pancreatitis, as well as autoimmune cholestasis, since no obstructive factor was identified on imaging. Type 1 autoimmune pancreatitis related to immunoglobulin G4 was also considered.

An investigation for autoimmune diseases was initiated, including antimitochondrial antibody, anti-smooth muscle antibody, anti-liver kidney microsomal type 1 antibody, antinuclear antibody, anti-Ro, anti-La, and serum immunoglobulins. All autoantibodies were negative. Immunoglobulin G was mildly elevated at 1,703 mg/dL, while immunoglobulin G4 levels were within the normal range.

Magnetic resonance cholangiopancreatography showed only mild intrahepatic bile duct dilation, without a typical pattern of PSC. Therefore, the diagnostic hypotheses of PSC and primary biliary cholangitis were initially considered unlikely.

Figure 5

Magnetic resonance cholangiopancreatography demonstrating mild intrahepatic bile duct dilation



Symptomatic treatment with ursodeoxycholic acid, corticosteroids, and antihistamines was initiated, with partial improvement of pruritus. The patient was subsequently discharged.

Diagnostic Clarification

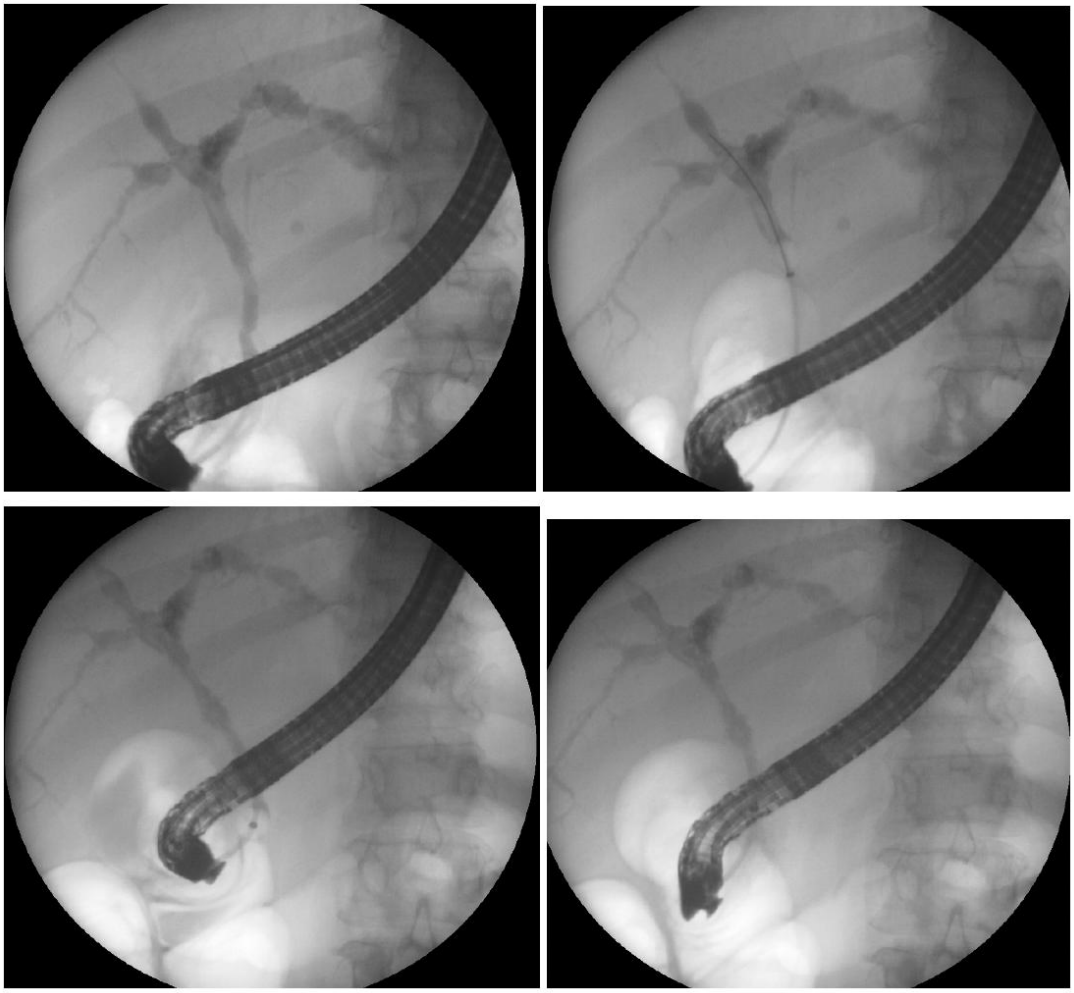
Given the negative autoantibody profile and the absence of suggestive anatomical findings on magnetic resonance cholangiopancreatography, the hypotheses of PSC and primary biliary cholangitis were initially excluded.

The patient continued to present with a cholestatic laboratory pattern and jaundice, and ERCP was therefore indicated. After an initially unsuccessful attempt, the examination was performed and demonstrated multifocal strictures and irregularities of the bile ducts compatible with PSC. Endoscopic papillotomy was performed.

The patient was referred to a specialized hepatology center for liver transplantation assessment.

Figure 6

Endoscopic retrograde cholangiopancreatography demonstrating an irregular common bile duct and common hepatic duct, with areas of stenosis throughout their course. The right and left hepatic ducts and biliary tree showed alternating strictures and dilations, producing a beaded appearance

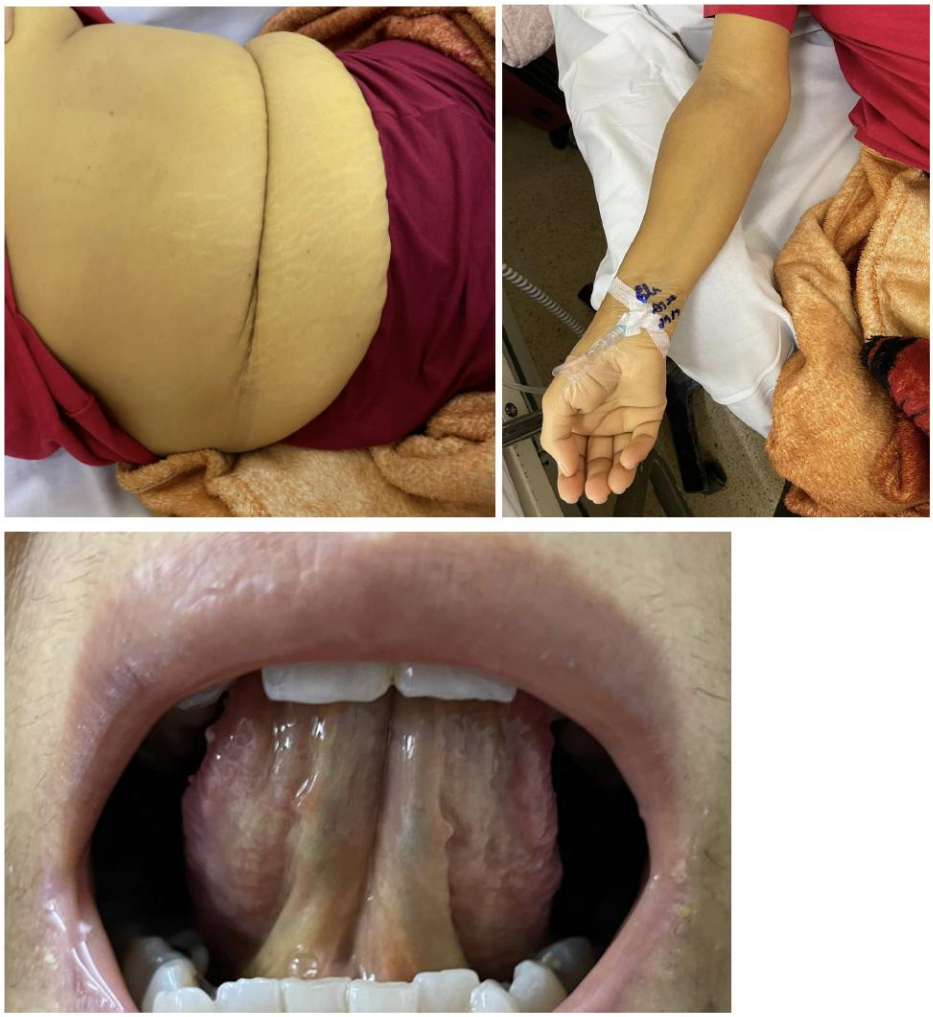


Third Hospitalization: Severe Acute Cholangitis

The patient returned with fever of 38 °C, asthenia, worsening jaundice, choluria, and right flank pain. On physical examination, she was hypotensive, with blood pressure of 80 × 60 mmHg, febrile at 39 °C, and in poor general condition.

Figure 7

Jaundice involving the trunk, right upper limb, and sublingual region



Laboratory tests showed total bilirubin of 17.6 mg/dL, direct bilirubin of 13.74 mg/dL, C-reactive protein of 164 mg/L, international normalized ratio of 1.68, and leukocytosis with left shift.

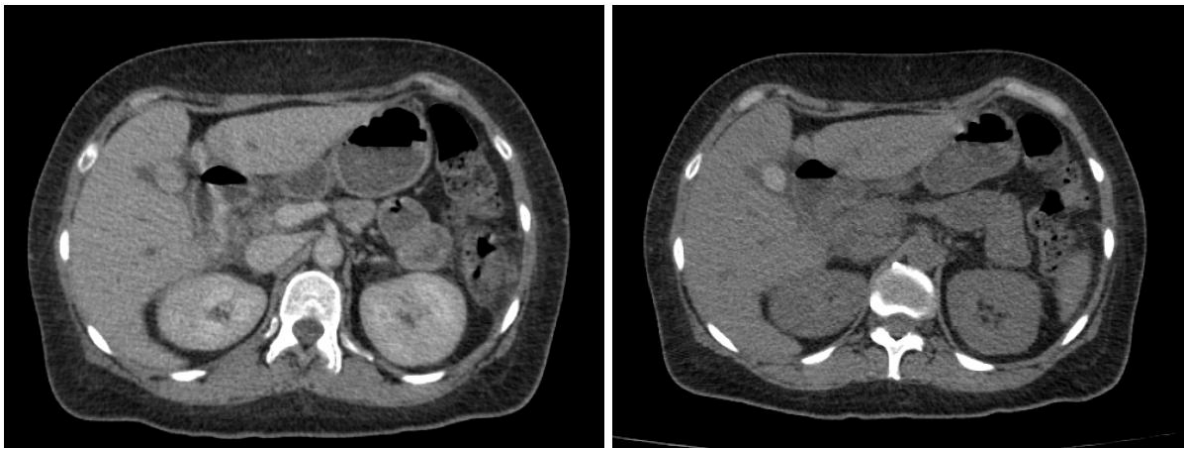
The diagnosis of acute cholangitis superimposed on PSC was established and classified as Tokyo grade III. The patient was transferred to the emergency room, received fluid resuscitation, norepinephrine infusion, and antibiotic therapy with ceftriaxone and metronidazole, and was then transferred to the intensive care unit.

She evolved with clinical and hemodynamic improvement, allowing discontinuation of vasopressor therapy and subsequent transfer to the ward. Due to new febrile episodes, antibiotic therapy was escalated to piperacillin-tazobactam.

Abdominal computed tomography demonstrated intrahepatic bile duct dilation, periportal edema, and pneumobilia.

Figure 8

Contrast-enhanced abdominal computed tomography demonstrating intrahepatic bile duct dilation, periportal edema, and pneumobilia



The patient showed progressive laboratory improvement, with reduction of bilirubin levels and inflammatory markers. She was discharged with scheduled outpatient follow-up and ongoing liver transplantation assessment.

5 DISCUSSION

Primary sclerosing cholangitis is a rare chronic cholestatic liver disease characterized by multifocal involvement of the intrahepatic and/or extrahepatic bile ducts due to inflammation, fibrosis, and stricturing. Although rare, its incidence has increased in recent years, ranging from 0.91 to 1.3 cases per 100,000 person-years, with male predominance and a mean age at diagnosis of approximately 40 years. (NICOLETTI; MAURICE; THORBURN, 2020)

PSC is frequently associated with other immune-mediated diseases, particularly inflammatory bowel disease (IBD). Approximately 70% to 80% of patients with PSC have IBD, with ulcerative colitis representing the most common association. Conversely, only a minority of patients with IBD develop PSC. For this reason, colonoscopy is recommended at the time of PSC diagnosis even in asymptomatic patients, and, when normal, should be repeated every three to five years. Patients with both PSC and IBD should undergo annual colorectal cancer surveillance. (BARBERIO et al., 2021)

The patient described in this report had no diagnosis of IBD, which may have contributed to diagnostic difficulty and delay. In patients with PSC, especially those with ulcerative colitis, atypical perinuclear anti-neutrophil cytoplasmic antibody may be present in a substantial proportion of cases. However, this marker is nonspecific for both PSC and IBD. In PSC and ulcerative colitis, atypical perinuclear anti-neutrophil cytoplasmic antibody shows

an immunofluorescence pattern similar to conventional perinuclear anti-neutrophil cytoplasmic antibody, but it is not directed against the classic myeloperoxidase target observed in vasculitis. In clinical practice, this antibody may support diagnostic suspicion but does not correlate with disease severity or prognosis. Importantly, PSC remains a radiological rather than a serological diagnosis. (CHAPMAN et al., 2019)

Several factors made the present case atypical and diagnostically challenging. From the outset, the epidemiological profile was unusual, as PSC is classically more common in men than in women. In addition, the absence of IBD removed one of the most common clinical associations that frequently prompts earlier suspicion of PSC.

Another important factor that complicated the diagnosis was the negative autoantibody profile. At least one autoantibody has been reported in a high proportion of patients with PSC. The most commonly observed autoantibodies include anti-smooth muscle antibodies and antinuclear antibodies, the latter being reported in up to 75% of patients. Perinuclear anti-neutrophil cytoplasmic antibody and anti-P40 autoantibodies may also be detected in approximately 30% to 80% of cases. Therefore, the complete absence of autoantibody positivity in this patient reinforces the atypical nature of her presentation. (GOCHANOUR; JAYASEKERA; KOWDLEY, 2020)

The patient also underwent magnetic resonance cholangiopancreatography, which demonstrated only mild intrahepatic bile duct dilation, predominantly in the left hepatic lobe, without extrahepatic bile duct dilation and with usual biliary branching. The combination of non-diagnostic cholangiographic findings and negative autoantibodies initially led clinicians away from the diagnosis of PSC, contributing to diagnostic delay. Typical magnetic resonance findings compatible with PSC include multifocal annular strictures of the intrahepatic and/or extrahepatic bile ducts, alternating with normal or mildly dilated biliary segments, as well as diffuse involvement of the hepatobiliary system, which may include the gallbladder, cystic duct, and pancreatic duct. (VENKATESH et al., 2021)

Historically, ERCP was considered the initial diagnostic procedure of choice for PSC. However, over the last decade, magnetic resonance cholangiopancreatography has become the preferred diagnostic method because of its comparable specificity, generally above 90%, and sensitivity, usually between 80% and 90%, in addition to being less invasive, less costly, and associated with fewer complications. In the present case, however, ERCP proved decisive, as it was the only method capable of establishing the diagnosis. (GIDWANEY; PAWA; DAS, 2017)

Given the broad spectrum of autoimmune hepatobiliary disorders, exclusion of alternative etiologies and careful differential diagnosis were essential during the patient's

evaluation. PSC may overlap with, or be associated with, other autoimmune liver diseases. The most common overlap in this context is PSC with features of autoimmune hepatitis, reported in approximately 17% of patients. (COUTO et al., 2019)

After exclusion of obstructive causes in the presence of a laboratory pattern suggestive of cholestasis, the patient underwent investigation for autoimmune etiologies. Anti-liver kidney microsomal type 1 antibody, antimitochondrial antibody, and anti-smooth muscle antibody were negative, which helped exclude other autoimmune causes, such as primary biliary cholangitis and autoimmune hepatitis.

PSC may also be confused with secondary sclerosing cholangitis, making this differential diagnosis essential. Secondary causes include ischemic injury to the bile ducts, biliary trauma, infectious conditions such as human immunodeficiency virus, cytomegalovirus, cryptococcosis, and mycobacterial infections, especially in immunosuppressed patients, as well as infiltrative diseases, among others. In the present case, these causes were excluded through appropriate serological testing and imaging studies.

Another particularly important differential diagnosis is immunoglobulin G4-related sclerosing cholangitis, a chronic inflammatory disease of the bile ducts mediated by immune mechanisms and included within the spectrum of immunoglobulin G4-related disease. This condition more frequently affects men over 50 years of age and is commonly associated with type 1 autoimmune pancreatitis. Distinguishing PSC from immunoglobulin G4-related sclerosing cholangitis is essential because treatment and prognosis differ substantially. Serum immunoglobulin G4 levels are elevated in approximately 50% to 60% of patients with immunoglobulin G4-related cholangitis, although normal levels do not exclude the disease and isolated elevation does not confirm the diagnosis. In PSC, immunoglobulin G4 levels are usually normal. Moreover, immunoglobulin G4-related cholangitis is not typically associated with the same autoantibody profile seen in PSC, such as perinuclear anti-neutrophil cytoplasmic antibody. (COUTO et al., 2019)

There are also important imaging differences between the two conditions. ERCP and magnetic resonance cholangiopancreatography are the preferred imaging modalities for evaluating both diseases. In PSC, strictures are usually short, multiple, and arranged in a beaded pattern, with diffuse intrahepatic involvement. In immunoglobulin G4-related cholangitis, strictures are generally long and continuous, with symmetric bile duct wall thickening and predominance in the distal common bile duct. When histopathology is available, immunoglobulin G4-related cholangitis is characterized by a lymphoplasmacytic infiltrate rich in immunoglobulin G4-positive plasma cells and storiform fibrosis. In PSC,

nonspecific portal inflammation and concentric periductal fibrosis are more commonly observed. Although histology may be confirmatory, it is not always necessary, as illustrated by the present case. (CHARATCHAROENWITTHAYA et al., 2008)

Patients with immunoglobulin G4-related cholangitis typically respond well to corticosteroid therapy, whereas this response is absent in PSC, which is associated with a higher risk of cholangiocarcinoma and a poorer prognosis. (NICOLETTI; MAURICE; THORBURN, 2020)

PSC is frequently associated with several complications, including cholelithiasis, cholestasis, cholangitis, dominant strictures, portal hypertension, liver failure, and malignancies such as cholangiocarcinoma and colorectal cancer. The present patient developed severe acute pancreatitis, an infectious and inflammatory complication that may obscure the classic presentation of PSC and lead to alternative diagnostic hypotheses, such as autoimmune pancreatitis or biliary obstruction secondary to pancreatic inflammation. Although sporadic associations between PSC and pancreatitis have been described, this finding remains uncommon in the literature, and its pathophysiological mechanisms are not fully defined. In this context, early diagnosis is essential to guide management and attempt to delay disease progression while preventing severe complications.

Despite advances in research, no treatment has been proven to slow disease progression. However, in advanced disease, favorable outcomes may be achieved after liver transplantation, which is indicated in patients with decompensated liver failure, severe complications such as recurrent bacterial cholangitis or intractable pruritus, and significantly impaired quality of life. (BOWLUS et al., 2023; LINDOR et al., 2009) In the present case, the patient required transplantation assessment within a relatively short time, representing a more accelerated course than that frequently described in the literature and highlighting the individual variability and potential influence of still poorly understood factors in the natural history of PSC. (LEE; KAPLAN, 1995; HIRSCHFIELD et al., 2011)

Several immunosuppressive agents have been studied for the treatment of PSC, although none has demonstrated conclusive benefit. Ursodeoxycholic acid remains the most extensively studied medication in this setting. Doses of up to 15 mg/kg/day may improve cholestatic biochemical markers by protecting bile ducts from cytotoxic hydrophobic bile acids, stimulating hepatobiliary secretion, and protecting hepatocytes from bile acid-induced apoptosis. However, despite its biochemical effects, ursodeoxycholic acid has not demonstrated improved survival or delayed need for liver transplantation. Studies have also failed to demonstrate benefit in preventing cholangiocarcinoma. Evidence suggests that discontinuation of ursodeoxycholic acid may be associated with worsening biochemical tests,

including alkaline phosphatase, bilirubin, gamma-glutamyltransferase, aspartate aminotransferase, and alanine aminotransferase, as well as worsening pruritus. Its use remains controversial, particularly regarding daily dosage, which varies across guidelines. (LEE; KAPLAN, 1995)

Regarding corticosteroids, their chronic use is not only ineffective in PSC but may also lead to bone loss and osteoporosis. Other agents, including cyclosporine, tacrolimus, methotrexate, azathioprine, anti-tumor necrosis factor therapy, and oral vancomycin, have been investigated, but available results remain inconsistent and uncertain. (KAPLAN, 1991)

In summary, this case contributes to the literature in several ways. It reinforces the importance of clinical and radiological suspicion even in the absence of typical serological findings, helping avoid diagnostic delay. It also highlights that although perinuclear anti-neutrophil cytoplasmic antibody is common in PSC, its absence does not exclude the diagnosis. PSC should therefore be understood as an immune-mediated disease whose diagnosis depends primarily on clinical and cholangiographic correlation rather than autoantibody positivity alone.

Furthermore, this case emphasizes the importance of investigating persistent chronic cholestasis even when magnetic resonance cholangiopancreatography is initially inconclusive and autoantibodies are negative. In general, the report contributes to reducing the underdiagnosis of atypical PSC and supports the role of ERCP in selected cases with persistent clinical suspicion despite non-diagnostic noninvasive imaging.

6 CONCLUSION

This case demonstrates that PSC may present with uncommon clinical manifestations, such as severe acute pancreatitis and absence of specific autoantibodies, and that these findings do not exclude the diagnosis. Maintaining diagnostic suspicion is essential to avoid delayed recognition of a disease with potentially severe prognosis. (KARLSEN et al., 2017; LINDOR et al., 2009)

In the present case, the definitive diagnosis of PSC was established only months after symptom onset, illustrating the prolonged diagnostic pathway that may occur in rare diseases with atypical presentation. The literature supports that, in cases of persistent cholestasis without an evident cause and with initially inconclusive cholangiographic findings, diagnostic suspicion should remain high, and repeat cholangiographic studies or directed invasive procedures may be required. (CHAPMAN et al., 2019; MINTZIRAS et al., 2016)

Another important contribution of this case is its emphasis on severe infectious complications, especially recurrent acute bacterial cholangitis classified as severe according

to the Tokyo criteria, which represents one of the major causes of morbidity in PSC and requires broad-spectrum antibiotic therapy and intensive supportive care. (BOWLUS et al., 2023)

Early diagnosis and stage-appropriate treatment may reduce the occurrence of PSC-related complications, including cholangitis, increased risk of biliary tract malignancy, cirrhosis, and liver failure. (EATON et al., 2018; BERNTSEN et al., 2019) Finally, it should be emphasized that delayed recognition may shorten the interval to liver transplantation, as occurred in the present case, in which transplantation assessment became necessary less than one year after the onset of clinical manifestations. (BOBERG et al., 2015)

Therefore, this report reinforces the need to improve diagnostic strategies and develop more accurate diagnostic algorithms for PSC, especially in patients with atypical phenotypes. Such approaches may help reduce diagnostic delay, improve early management, and potentially optimize prognosis in patients with non-classical presentations of the disease.

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